YORK ACADEMY OF SCIENCES

otechnology, National Library of

tion-deficit hyperactivity disorder.
77–184.
. Scand. **36**(Suppl.): 129.
l other neurophysiological abnor-

of renal disease. Neurol. Clin. **7:**

kidney. J. Neurol. Neurosurg. Psy-

5. Nutrition, growth and neurointe-
gic study. Pediatrics **38** (Suppl.):

5. Auditory brain stem responses in
0.
al. 1991. The brainstem reticular
0.
uman Gene Map. National Center
Web Site.
y association between HLA-DR2

sy. Trends Neurosci. **14:** 235–239.

Brain Imaging of Attention Deficit/Hyperactivity Disorder

JAY N. GIEDD, JONATHAN BLUMENTHAL, ELIZABETH MOLLOY, AND F. XAVIER CASTELLANOS

Child Psychiatry Branch, National Institute of Mental Health, Bethesda, Maryland 20892, USA

ABSTRACT: **Advances in imaging technology allow unprecedented access to the anatomy and physiology of the living, growing human brain. Anatomical imaging studies of individuals with attention deficit/hyperactivity disorder (ADHD) consistently point to involvement of the frontal lobes, basal ganglia, corpus callosum, and cerebellum. Imaging studies of brain physiology also support involvement of right frontal-basal ganglia circuitry with a powerful modulatory influence from the cerebellum. Although not currently of diagnostic utility, further extension and refinement of these findings may offer hope for greater understanding of the core nature of ADHD and possible subtyping to inform treatment interventions.**

KEYWORDS: **ADHD; Magnetic resonance imaging; Child; Adolescent; Development.**

INTRODUCTION

Family,[1,2] twin,[3,4] and adoption[5] studies all support a biological basis for attention deficit/hyperactivity disorder (ADHD), although identification of the specific neuroanatomical substrates have only been possible with recent advances in neuroimaging. Early ADHD imaging studies using computerized tomography were limited by lack of quantitative measures, poor spatial resolution, and relatively small sample sizes of inconsistently characterized subjects. Also, the use of ionizing radiation in these technologies precludes their ethical use in healthy children, making it difficult to acquire valid comparison groups. It is not surprising then that the results of these early studies, summarized in TABLE 1, are inconsistent with later findings.

Magnetic resonance imaging (MRI), with its lack of ionizing radiation and capacity to provide exquisite anatomical detail, is the imaging modality of choice for pediatric studies. The safety of the procedure allows not only scans of children but also even repeated scans of the same children over time. This capacity for longitudinal studies is critical to exploring maturational trajectories of the developing human brain. Anatomic MRI studies have found anomalies in total cerebral volume, corpus callosum, basal ganglia, and cerebellum. Results of ADHD MRI studies are summarized in TABLE 2.

Functional imaging studies, including those using positron emission tomography (PET), functional MRI, and Xenon inhalation, generally support the anatomical

Address for correspondence: Jay N. Giedd, M.D., Child Psychiatry Branch, National Institute of Mental Health, Building 10, Room 4C110, 10 Center Drive, MSC 1367, Bethesda, MD 20892. Voice: 301 435-4517; fax: 301 480-8898.
jgiedd@helix.nih.gov

TABLE 1. Computerized tomography studies of attention deficit/hyperactivity disorder

Study	Patients	Control Subjects	Findings	Comments
Bergstrom & Bille, 1978[65]	46 (minimal brain dysfunction)	None	33% had "abnormal" ventricles	Qualitative; criteria unspecified, no contrast group; diagnosis vague
Thompson *et al.*, 1980[66]	44 (minimal brain dysfunction)	None	4.5% abnormal	Diagnosis heterogeneous; quantitative measures, no contrast group
Caparulo *et al.*,1981[67]	14 (DSM-3 ADD)	None	28% abnormal	Structured interviews for diagnosis; qualitative measures; no contrast group
Reiss *et al.*, 1983[68]	7 (DSM-3 ADD)	19 (Neurological patients)	VBR larger	Quantitative; results not given for ADD subgroup
Shaywitz *et al.*, 1983[22]	35 (DSM-3 ADD)	27	None	Quantitative
Nasrallah *et al.*, 1986[32]	24 (Hyperkinetic/ minimal brain dysfunction)	27	None	No quantitative differences

implications of dysfunction in neural circuitry involving the frontal lobes, striatum, and cerebellum. Results of functional imaging studies are summarized in TABLE 3.

ANATOMIC BRAIN IMAGING STUDIES OF ADHD

Total Cerebral Volume

Although the total size of the human brain is already 90–95% that of an adult by first grade,[6–9] the subcomponents of the brain continue to undergo dynamic changes throughout childhood and adolescence. White matter volume increases linearly, reflecting increasing myelination,[10] and gray matter volume increases until early-to-mid-adolescence before decreasing during late adolescence, presumably from continued synaptic pruning.[11,12] Brain size is highly variable with as much as a twofold difference even among healthy people matched for age, sex, height, and weight.[13] Total brain size in ADHD subjects is approximately 5% smaller than in age- and gender-matched controls.[14] Thus, analyses of regional brain abnormalities should also control statistically for differences among individuals in total brain volume, preferably by using analyses of covariance rather than simple ratios or proportions,[15] although most of the studies summarized below have not done so.

TABLE 2. Magnetic resonance imaging studies of attention deficit/hyperactivity disorder

Study	Patients/	Findings	Comments

n deficit/hyperactivity disorder

Findings	Comments
33% had "abnormal" ventricles	Qualitative; criteria unspecified, no contrast group; diagnosis vague
4.5% abnormal	Diagnosis heterogeneous; quantitative measures, no contrast group
28% abnormal	Structured interviews for diagnosis; qualitative measures; no contrast group
VBR larger	Quantitative; results not given for ADD subgroup
None	Quantitative
None	No quantitative differences

ving the frontal lobes, striatum,
es are summarized in TABLE 3.

UDIES OF ADHD

e

ady 90–95% that of an adult by
ue to undergo dynamic changes
ter volume increases linearly,
volume increases until early-to-
cence, presumably from contin-
e with as much as a twofold dif-
sex, height, and weight.[13] Total
maller than in age- and gender-
abnormalities should also con-
total brain volume, preferably
atios or proportions,[15] although
so.

TABLE 2. Magnetic resonance imaging studies of attention deficit/hyperactivity disorder

Study	Patients/ Controls	Findings	Comments
Hynd *et al.*, 1990[23]	10/10	Normal R > L anterior frontal width reversed in ADHD	Only a single axial slice. First MRI study in ADHD
Hynd *et al.*, 1991[69]	7/10	Anterior and posterior corpus callosum areas smaller in ADHD	Small study, individual region differences not significant
Hynd *et al.*, 1993[70]	11/11	L caudate wider than R in normal subjects; reversed in ADHD	"Best" axial slice measured, high variability
Giedd *et al.*, 1994[17]	18/18	Rostrum, rostral body of corpus callosum smaller in ADHD	Rostral body correlated significantly with hyperactivity ratings
Castellanos *et al.*, 1994[17]	50/48	Right caudate smaller and loss of normal R > L caudate asymmetry in ADHD	Supports developmental abnormalities of frontal-striatal circuits in ADHD
Semrud-Clikeman *et al.*,1994[19]	15/15	Splenium (posterior corpus callosum) significantly smaller in ADHD group	Difference not significant in 10 stimulant responders
Baumgardner *et al.*, 1996[18]	13/27	Rostral body of corpus callosum smaller in ADHD	
Aylward *et al.*, 1996[71]	10/11	Globus pallidus smaller in ADHD (significant on left).	Caudate and putamen also smaller in ADHD, although not significantly
Castellanos *et al.*, 1996[14]	57/55	Total cerebral volume, caudate, globus pallidus smaller in ADHD	Supports right prefrontal-striatal-cortical circuitry dysfunction in ADHD
Filipek *et al.*, 1997[24]	15/15	Caudates and right anterior superior white matter smaller in ADHD; posterior white matter volumes decreased only in stimulant non-responders.	First study to quantify gray and white matter separately. Authors suggest using medication response to subtype patient groups
Casey *et al.*, 1997[72]	26/26	Performance on response inhibition tasks correlate with anatomical measures of frontostriatal circuitry, particularly on right.	Suggests a role of the right prefrontal cortex in suppressing responses while the basal ganglia appear to be involved in executing these behavioral responses
Mataro *et al.*, 1997[73]	11/19	Larger right caudate	Single-slice transversal measurements of the head of the caudate nucleus
Berquin *et al.*, 1997[33]	46/47	Smaller posterior inferior cerebellar vermal volume	Replicated finding
Mostofsky *et al.*, 1998[34]	12/23	Smaller posterior inferior cerebellar vermal volume	Replicated finding

TABLE 3. Single photon emission tomography studies using inhaled ^{133}Xenon

Study	Patients	Control Subjects	Findings	Comments
Lou *et al.*, 1984[74]	$n = 13$ (1 F); 11 w/ mixed ADD; 8 "dysphasic"	$n = 9$, mostly siblings (3 F)	Frontal hypoperfusion in all ADD; caudate hypoperfusion in 7/11 w/ ADD; central perfusion increased in 6/6 after methylphenidate (MPH)	Contrast group 2.4 yrs older on average; ADD group very heterogeneous
Lou *et al.*, 1989[75]	$n = 6$ "pure ADHD"; $n = 13$ ADHD + other CNS dysfunction; 13 (includes 4 "pure ADHD") scanned pre- and post-MPH	same 9 contrast subjects as in Ref. 54	"Pure ADHD": decreased R striatal perfusion, increased occipital and L sensorimotor and auditory regions; MPH significantly increased L striatal perfusion.	Included 20 subjects from ref. 54; even "pure ADHD" group included measles encephalitis, neonatal cerebral ischemia
Lou *et al.*, 1990[44]	$n = 9$ "pure ADHD" (2 F); $n = 8$ ADHD + dysphasia; (0 F)	15 contrast subjects (6 new, 7 F)	Normalized striatal and posterior periventricular perfusion decreased in ADHD and ADHD+; occipital perfusion increased in "pure ADHD"	Included 23 subjects from ref. 56; results not reported by side; as in prior reports, subjects not matched by sex or age, due to ethical and practical constraints

Corpus Callosum

The corpus callosum is the largest interhemispheric commissure in the brain consisting of approximately 200 million mostly myelinated fibers connecting homologous areas of the left and right cerebral hemispheres. Because of the orientation and myelination of its fibers, the corpus callosum is readily identifiable on MR images and most research groups have started by quantifying its mid-sagittal area. Although total corpus callosum area has not differed from controls in any study, smaller anterior regions have generally been found[16–18] in ADHD subjects. The largest MRI study did not confirm these differences when measurements were obtained from images that did not control for the positioning of the brain.[14] However, reanalysis with images aligned to a standard orientation confirmed a smaller corpus callosum rostrum in ADHD [mean rostral area 25.5 mm^2 (SD = 10.3) in 50 boys with ADHD, versus 30.0 mm^2 (12.1) in 50 matched controls ($t = 1.98$, $df = 98$, $p = 0.05$, uncorrected) Castellanos *et al.*, 1999, unpublished data]. The rostrum is the most anterior (and inferior) portion of the corpus callosum, and nearly all findings in ADHD have been anterior. The one exception was based on 15 ADHD subjects that included five stimulant non-responders. The authors found that the subgroup of stimulant

sing inhaled ^{133}Xenon

	Comments
rfusion ıdate in 7/11 ıl perfu- n 6/6 enidate	Contrast group 2.4 yrs older on average; ADD group very heterogeneous
iatal eased nd s; MPH creased L n.	Included 20 subjects from ref. 54; even "pure ADHD" group included measles encephalitis, neonatal cerebral ischemia
atal and ntricu- creased ADHD+; ion ure	Included 23 subjects from ref. 56; results not reported by side; as in prior reports, subjects not matched by sex or age, due to ethical and practical constraints

ic commissure in the brain con-
ated fibers connecting homolo-
. Because of the orientation and
dily identifiable on MR images
g its mid-sagittal area. Although
trols in any study, smaller ante-
HD subjects. The largest MRI
surements were obtained from
ne brain.[14] However, reanalysis
med a smaller corpus callosum
= 10.3) in 50 boys with ADHD,
1.98, df = 98, $p = 0.05$, uncor-
The rostrum is the most anterior
l nearly all findings in ADHD
15 ADHD subjects that included
that the subgroup of stimulant

non-responders had the smallest splenium area.[19] Examination of their data shows that their finding of a difference in the posterior corpus callosum would not have reached significance without the inclusion of those five subjects. Given the known heterogeneity and comorbidity of ADHD, we can speculate that posterior brain changes may be associated with ADHD symptoms secondary to a learning disability, which would explain the absence of benefits from stimulant treatment. For example, in a sample of prematurely born children, posterior ventricular enlargement and posterior periventricular leukomalacia were associated with worse performance on spatial and visuoperceptual abilities, but not with behavioral problems such as hyperactivity.[20]

Prefrontal Brain

Smaller anterior corpus callosal areas are consistent with involvement of prefrontal cortical regions. Normally, the right anterior brain is slightly but consistently larger than the left.[21] Significant decreases of this asymmetry in ADHD have been reported using computed tomography[22] and MRI.[9,14,23,24] Volumetric measures have also detected smaller right-sided prefrontal brain regions measured "en bloc"[14,24] in boys with ADHD which were correlated with neuropsychological performance on tasks that required response inhibition.[25] In the only published study to date to report gray-white segmentation, right anterior white matter was also reduced in ADHD boys.[24] However, this difference must be interpreted with caution since the patient group was two years younger on average than the controls ($p = 0.12$, $n = 15$ per group) and since white matter volume increases linearly with age within this age range.[9,10]

Caudate Nucleus

The caudate nucleus and its associated circuits have long been suspected to play a pivotal role in ADHD.[26] Abnormalities of caudate nucleus volume[14,24] or asymmetry[14,27,28] have been reported although the studies differ in whether the normal caudate is asymmetric, and whether this asymmetry normally favors the right[14] or the left caudate.[24,28,27] These inconsistencies may reflect differences in methodology and comorbidity. For example, the mean coefficient of variation in the two studies that used single-slice area measures of the caudate[27,28] was 0.22 (SD 0.04), which is significantly greater than the coefficient of variation in the studies that reported volumes[14,24] (mean 0.14, SD 0.03, t = 3.20, df = 6, $p = 0.02$).

Putamen

Neither of the anatomic MRI studies that reported putamen volumes detected significant diagnostic group differences[14,29] although statistical power was insufficient in one study to rule out type II error.[29] It is worth noting that anatomic neuroimaging findings in Tourette syndrome have centered on the putamen,[30,31] the striatal region associated with primary and supplementary motor areas.

Globus Pallidus

The output nuclei of the basal ganglia are the internal segment of the globus pallidus and the substantia nigra pars reticulata, but the volume of the latter cannot generally be measured with MRI, and the size of the globus pallidus can only be measured as a unit (lateral and medial segments together), and then only with difficulty. Still, this region has been found to be significantly reduced in size in ADHD subjects,[14,29] although these two studies differed in finding the larger difference on the left and right sides, respectively.

Cerebellum

An early computed tomography study found a trend towards greater cerebellar atrophy in adults with a prior history of hyperkinetic minimal brain dysfunction.[32] In a quantitative study of 112 subjects, the volumes of the cerebellar hemispheres were found to be significantly smaller in ADHD boys.[14] In a follow-up study within the same sample, the cerebellar vermis as a whole, and particularly the posterior-inferior lobules (lobules VIII–X) were found to be significantly smaller in ADHD.[33] It is speculated that dysfunction of the cerebello-thalamo-prefrontal circuit may underlie the motor control, inhibition, and executive function deficits encountered in ADHD.

Smaller lobules VIII–X were independently replicated in ADHD,[34] but also in childhood-onset schizophrenia[35] and in multiple-episode adult bipolar disorder patients,[36] demonstrating once again the non-specificity of most anatomic deviations. Despite the caveats, there is increasing interest in understanding the role of the cerebellum in non-motor domains such as cognition[37] and in the modulation of emotions.[38]

FUNCTIONAL BRAIN IMAGING STUDIES OF ADHD TABLES 4–6

PET with [^{18}F]-fluoro-2-deoxy-D-glucose (FDG) was used to demonstrate decreased frontal cerebral metabolism in adults with ADHD,[39] although inconsistent results in adolescents[40–42] led the authors to explore other techniques in ADHD.[43] Other investigators have measured local cerebral blood flow, which is closely linked to neuronal activity and tissue metabolism, with a variety of techniques including ^{133}Xenon inhalation and single-photon emission tomography. Decreased blood flow has been found in ADHD subjects in the striatum[44] and in prefrontal regions.[45] However, these results must be interpreted cautiously because ethical constraints make it difficult to obtain truly independent observations from normal control children. A more promising technique is blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI), which obviates the need to use ionizing radiation.

The BOLD fMRI technique was used in a study of 10 boys with ADHD and 6 controls, all of whom were scanned on and off methylphenidate while they performed Go No-Go tasks.[46] The authors extended to methylphenidate the observation that stimulants improve performance in normal children as they do in patients with ADHD.[47] In caudate and putamen, Vaidya and colleagues found a striking group difference. In the task with the faster stimulus presentation rate, methylphenidate

allidus

e the internal segment of the globus pal-
, but the volume of the latter cannot gen-
ze of the globus pallidus can only be
ients together), and then only with diffi-
e significantly reduced in size in ADHD
ffered in finding the larger difference on

llum

found a trend towards greater cerebellar
perkinetic minimal brain dysfunction.[32]
e volumes of the cerebellar hemispheres
DHD boys.[14] In a follow-up study within
a whole, and particularly the posterior-
d to be significantly smaller in ADHD.[33]
erebello-thalamo-prefrontal circuit may
executive function deficits encountered in

ently replicated in ADHD,[34] but also in
multiple-episode adult bipolar disorder
n-specificity of most anatomic deviations.
rest in understanding the role of the cere-
ion[37] and in the modulation of emotions.[38]

GING STUDIES OF ADHD
ES 4–6

e (FDG) was used to demonstrate decreased
ADHD,[39] although inconsistent results in
ther techniques in ADHD.[43] Other investi-
flow, which is closely linked to neuronal
y of techniques including ^{133}Xenon inhala-
hy. Decreased blood flow has been found
prefrontal regions.[45] However, these results
ical constraints make it difficult to obtain
l control children. A more promising tech-
nt (BOLD) functional magnetic resonance
use ionizing radiation.
in a study of 10 boys with ADHD and 6
and off methylphenidate while they per-
tended to methylphenidate the observation
ormal children as they do in patients with
and colleagues found a striking group dif-
nulus presentation rate, methylphenidate

increased the number of activated pixels in caudate and putamen in ADHD subjects, but it had the opposite effect in the controls. In both caudate and putamen, controls activated significantly fewer pixels when scanned while on methylphenidate compared to drug-free scans. Perhaps equally interesting was the finding that patients as well as controls activated significantly larger numbers of pixels in prefrontal cortex on drug. This regional dissociation between prefrontal cortex and striatum is consistent with the finding that ventral tegmental area dopaminergic neurons, which mostly innervate prefrontal cortex, lack autoreceptors, while nigrostriatal dopamine neurons have abundant numbers of autoreceptors.[48] Differences in neuronal autoreceptor regulation have been hypothesized to underlie the therapeutic effects of psychostimulants,[49–51] and the pattern of findings in the normal controls fits the prediction that methylphenidate would increase activation in prefrontal neurons by increasing synaptic and extrasynaptic dopamine levels; however, it would have the reverse effect in the striatum by producing a regulatory inhibition of firing. If replicated, these findings suggest that ADHD children differ qualitatively in striatal dopamine regulation and that such a difference may reflect etiological factors. However, before accepting this interpretation, we must note that all the patients had been medicated with methylphenidate until 36 hours prior to their scans. Since the normal controls had by definition never been previously exposed to stimulants, the possibility that these findings reflect medication withdrawal effects must first be excluded in replications and extensions of this work.

Frontal striatal circuits were targeted in another fMRI study using a sample of 7 adolescent boys with ADHD who were unmedicated or medication free for at least one week before scanning and 9 controls.[52] Subjects were scanned while performing the Stop Task[53] and a delay task that required synchronization of a motor response to an intermittently appearing visual stimulus. The hyperactive subjects showed less brain activity, predominantly in the right medial frontal cortex during both tasks, and in the right inferior prefrontal cortex and left caudate nucleus during the Stop Task. They concluded, "the right inferior frontal lobe — and its projections to the caudate — has been related to response inhibition.... It thus seems that the brake system of the brain is localized to the right prefrontal lobe, and its underactivation in ADHD seems to be the neural correlate of a less efficient inhibitory motor control"[52] (p. 895).

The principal limitation of fMRI explorations of ADHD is the exquisite sensitivity of the technique to even minimal movement during scanning. Vaidya and colleagues[46] found that using a bite-bar was essential in their study of children with ADHD and child controls. Rubia *et al.*[52] included only adolescents who were able to remain sufficiently immobile in the scanner. Because physical restlessness decreases with age,[54] Bush and colleagues[55] studied eight adults who had a history of childhood onset and persistence into adulthood of ADHD and eight matched controls using the Counting Stroop during fMRI. The Counting Stroop was used to avoid verbal responses; rather than color words, subjects were shown words that were repeated one to four times per presentation. Subjects were required to press the button corresponding to the number of words, and presenting number words that did not match the number of presented words provided interference.[56] Although both groups of subjects showed the expected slowing of response times in the interference condition, significant activation of bilateral anterior cingulate was only found in the normal controls. In contrast, ADHD subjects significantly activated right and

TABLE 4. Positron emission tomography studies of glucose cerebral metabolism

Study	Patients	Control Subjects	Findings	Comments
Zametkin *et al.*, 1990[39]	25 adults (7 F)	50 adults (22 F)	Global cerebral metabolism 8% lower in ADHD, with absolute significant decreases in 30 of 60 regions. Normalized differences all on left: superior posterior frontal, medial and anterior frontal and rolandic	Global and absolute differences in adults with childhood ADHD who were parents of children with ADHD not replicated in adolescents with ADHD
Zametkin *et al.*, 1993[40]	10 adolescents (3F)	10 adolescents (3F; 7 were siblings of ADHD probands, only 2 in this study)	No differences in global metabolism. Normalized metabolism decreased significantly in 6 regions and increased in 1 (see text)	The 3 ADHD females had 18% lower metabolism than 3 normal girls, but difference was not significant
Ernst *et al.*, 1994[41]	20 adolescents (6F); includes all subjects from ref. 40	19 adolescents (5F)	No group differences in global metabolism; metabolism significantly lower in 6 ADHD females than controls of either sex or ADHD boys	Significant global differences in small sample of females not confirmed in larger independent sample (see below)
Ernst *et al.*, 1996 (unpublished)	10 adolescent girls (independent sample)	11 adolescent girls, all unrelated to probands	No group differences in global metabolism; metabolism negatively correlated with sexual maturity in combined sample; normal (L>R) asymmetry reversed in ADHD in anterior putamen and sylvian region	Highlights relation between sexual development and cerebral metabolism. New findings of asymmetric metabolism in discrete regions will require replication with improved task

		in this study)		
Ernst *et al.*, 1994[41]	20 adolescents (6F); includes all subjects from ref. 40	19 adolescents (5F)	No group differences in global metabolism; metabolism significantly lower in 6 ADHD females than controls of either sex or ADHD boys	Significant global differences in small sample of females not confirmed in larger independent sample (see below)
Ernst *et al.*, 1996 (unpublished)	10 adolescent girls (independent sample)	11 adolescent girls, all unrelated to probands	No group differences in global metabolism; metabolism negatively correlated with sexual maturity in combined sample; normal (L>R) asymmetry reversed in ADHD in anterior putamen and sylvian region	Highlights relation between sexual development and cerebral metabolism. New findings of asymmetric metabolism in discrete regions will require replication with improved task

TABLE 5. Positron emission tomography studies of stimulant response in ADHD

Study	Method	Significant Increases	Significant Decreases	Comments
Matochik *et al.*, 1993[76]	Acute oral methylphenidate in 14 adults (3 F)	L posterior frontal (plane B) L parietal (plane B)	Anterior medial frontal (plane C) L parietal (plane C) L parietal/occipital (plane C)	No effect on continuous performance test (CPT), although subjective and cardiovascular effects significant.
Ibid.	Acute oral dextroamphetamine in 13 adults (4 F)	Anterior medial frontal (C)R posterior temporal (D) R thalamus R caudate	R rolandic (B) L anterior frontal (D) R anterior frontal (E)	CPT accuracy improved by drug, although did not correlate significantly with metabolism. Right caudate increase was the most pronounced.
Matochik *et al.*, 1994[77]	Chronic individually titrated methylphenidate in 19 adults (6 F)	R posterior frontal (E)	R anterior putamen (D)	No global effects; normalized results possibly type I error (2/60 uncorrected t-tests).
Ibid.	Chronic individually titrated dextroamphetamine in 18 adults (10 F)	none	none	Significant cardiovascular and psychological effects but no change in CPT or in any global or regional measures.
Ernst *et al.*, 1994[78]	Single-blind placebo and IV dextroamphetamine in 8 adults (3 F)	R parietal (C)	R anterior temporal (D) R hippocampus (E)	No net global effects (4 increased, 2 decreased, 2 unchanged).

TABLE 6. Functional imaging studies of cerebral blood flow in ADHD

Study	Method	Patients	Control Subjects	Findings	Comments
Amen *et al.*, 1994[45]	[^{99}m-TC] SPECT at rest & during math stress test	54 (8 F)	18 (8 F)	Prefrontal deactivation" significantly greater in ADHD (65% vs 5%)	Intriguing report; qualitative criteria not specified.
Sieg *et al.*, 1995[79]	[^{123}-I] SPECT at rest	10 (3 F)	6 (1 F)	Left (vs right) blood flow reduced in frontal and parietal regions in ADHD.	Groups differed significantly in age and IQ (controls 3 years older, mean IQ 15 points higher).
Schweitzer *et al.*, 1995[80]	[^{15}O] water PET, auditory addition task on 2 consecutive days	4 male adults	5 male adults	ADHD: activation of visual regions, vs. R parietal and L inferior frontal in controls; no improvement over time in ADHD.	Small sample. If confirmed with more subjects would suggest different, less effective (more visual) cognitive strategies used by ADHD subjects.
Teicher *et al.*, 1996[81]	T2* relaxation times with MRI	8 children	n.a.	Optimal dose methylphenidate significantly increased R caudate blood flow, decreased R frontal cortical flow.	Small sample; no activating task used.
Schweitzer *et al.*, 2000[82]	[^{15}O] water PET, neural activation related to working memory	6 male adults	6 male adults	Task-related changes in rCBF in the men without ADHD were more prominent in the frontal and temporal regions, but rCBF changes in men with ADHD were more widespread and primarily located in the occipital regions.	Small sample; suggests the use of compensatory mental and neural strategies by subjects with ADHD in response to a disrupted ability to inhibit attention to non-relevant stimuli and the use of internalized speech to guide behavior
Bush *et al.*, 1999[83]	fMRI, Counting Stroop	8 adults	8 adults	ADHD subjects failed to activate the anterior cingulate cogntive division (ACcd) during the Counting Stroop. ACcd activity higher in control group. ADHD subjects did activate a frontostriatal-insular network, indicating ACcd hypoactivity was not caused by globally poor neuronal responsiveness.	Small sample; supports a hypothesized dysfunction of the ACcd in ADHD.

Schweitzer *et al.*, 2000[82]	[^{15}O] water PET, neural activation related to working memory	6 male adults	6 male adults	Task-related changes in rCBF in the men without ADHD were more prominent in the frontal and temporal regions, but rCBF changes in men with ADHD were more widespread and primarily located in the occipital regions.	Small sample; suggests the use of compensatory mental and neural strategies by subjects with ADHD in response to a disrupted ability to inhibit attention to non-relevant stimuli and the use of internalized speech to guide behavior
Bush *et al.*, 1999[83]	fMRI, Counting Stroop	8 adults	8 adults	ADHD subjects failed to activate the anterior cingulate cogntive division (ACcd) during the Counting Stroop. ACcd activity higher in control group. ADHD subjects did activate a frontostriatal-insular network, indicating ACcd hypoactivity was not caused by globally poor neuronal responsiveness.	Small sample; supports a hypothesized dysfunction of the ACcd in ADHD.

TABLE 6/continued.

Study	Method	Patients	Control Subjects	Findings	Comments
Rubia *et al.*, 1999[52]	FMRI.	7 males	9 males	ADHD adolescents showed lower power of response in the right mesial prefrontal cortex during both tasks (stop task, requiring inhibition of a planned motor response, and a motor timing task, requiring timing of a motor response to a sensory cue) and in the right inferior prefrontal cortex and left caudate during the stop task.	Small sample; ADHD is associated with subnormal activation of the prefrontal systems responsible for higher-order motor control. Functional MRI is a feasible technique for investigation of neural correlates of ADHD.
Vaidya et al., 1998[46]	FMRI, two go/no-go tasks with and without drug	10 male children	6 male children	ADHD impaired inhibitory control on both tasks. Off-drug frontal-striatal activation during response inhibition differed between ADHD and healthy children. The drug modulated brain activation during response inhibition on only one task. In contrast, it increased striatal activation in ADHD children but reduced it in healthy children.	Small sample; suggests that ADHD is characterized by atypical frontal-striatal function and that methylphenidate affects striatal activation differently in ADHD than in healthy children

left inferior frontal gyrus, right and left insula, left caudate, right putamen, right thalamus, and left pulvinar. Thus, the absence of cingulate activation could not be ascribed to a simple failure to activate a neural network, although the authors noted that possible anatomic differences in cingulate volume, and stimulant medication history could have confounded their results. Also, the cognitive task did not result in sufficiently robust activation patterns to allow for single-subject analyses, which is typically a strong point of fMRI studies. Thus, absence of activation could simply reflect greater anatomic variability in the subjects with ADHD. Nevertheless, further exploration with this task and technique in younger subjects is clearly warranted.

Despite the natural advantages of magnetic resonance scanning for ADHD, PET still offers the only practical way of assaying the neurochemistry of the human brain *in vivo*. For example, [fluorine-18] fluorodopa ([^{18}F]F-DOPA) was used to label catecholamine terminals in 17 unmedicated adults with ADHD.[57] [^{18}F]F-DOPA uptake was significantly diminished in the left and medial prefrontal cortex of the ADHD adults compared to the 23 controls, with no differences in striatum or midbrain regions. By contrast, in 10 adolescents with ADHD, [^{18}F]F-DOPA uptake in right midbrain was significantly elevated compared to 10 controls ($p = .04$, uncorrected for multiple comparisons).[58] Taken together, these preliminary results further support the notion that catecholamine dysregulation is central to the pathophysiology of ADHD, and not just to its treatment. They also highlight the proposition that dopaminergic and noradrenergic systems cannot be understood without taking developmental effects into account.[49]

The utility of single-photon computed emission tomography, which is more available and less expensive than PET, was highlighted in an exciting preliminary report.[59] The highly selective dopamine transporter ligand [123]-I-Altropane was used in 6 adults with ADHD who were compared to a database of 30 healthy controls. Striatal binding potential (Bi_{max}/K_d) was elevated in all 6 ADHD patients, with each patient exceeding the mean values of the corresponding age-matched controls by at least 2 standard deviations. This finding, if replicated in a larger sample, will raise many questions. Will similar results be found in younger subjects? Are increased numbers of striatal dopamine transporters related to the etiology of ADHD, or to compensatory attempts at regulating striatal dopaminergic tone? Are the effects related to prior medication exposure?

SUMMARY

Taken together, the results of the imaging and neuropsychological studies suggest right frontal-striatal circuitry involvement in ADHD with a modulating influence from the cerebellum.[60] The cortico-striatal-thalamic circuits select, initiate, and execute complex motor and cognitive responses,[61] and cerebellar circuits provide online guidance of these functions.[62] Involvement of right frontal-striatal circuitry is supported by studies of non-human primates in which "lesions of the (frontal lobe) lateral surface appear to be effective in causing hyperactivity to the extent that they interfere with orbital and other projections passing to the caudate"[63] (p. 75) and by neuropsychological studies which demonstrate right-sided frontal-striatal dysfunction in ADHD.[64]

, left caudate, right putamen, right
of cingulate activation could not be
network, although the authors noted
volume, and stimulant medication
o, the cognitive task did not result in
for single-subject analyses, which is
absence of activation could simply
ts with ADHD. Nevertheless, further
nger subjects is clearly warranted.

resonance scanning for ADHD, PET
e neurochemistry of the human brain
([18F]F-DOPA) was used to label cat-
with ADHD.[57] [18F]F-DOPA uptake
edial prefrontal cortex of the ADHD
differences in striatum or midbrain
ADHD, [18F]F-DOPA uptake in right
to 10 controls ($p = .04$, uncorrected
these preliminary results further sup-
on is central to the pathophysiology of
highlight the proposition that dopam-
understood without taking develop-

ssion tomography, which is more avail-
ghlighted in an exciting preliminary
nsporter ligand [123]-I-Altropane was
pared to a database of 30 healthy con-
s elevated in all 6 ADHD patients, with
e corresponding age-matched controls
g, if replicated in a larger sample, will
be found in younger subjects? Are
ansporters related to the etiology of
ulating striatal dopaminergic tone? Are
ure?

RY

and neuropsychological studies suggest
in ADHD with a modulating influence
halamic circuits select, initiate, and exe-
es,[61] and cerebellar circuits provide on-
ment of right frontal-striatal circuitry is
s in which "lesions of the (frontal lobe)
sing hyperactivity to the extent that they
passing to the caudate"[63] (p. 75) and by
rate right-sided frontal-striatal dysfunc-

The theoretical implications of current anatomic findings in ADHD are tentative. Consistent replication by independent centers and quantification of finer cerebral subdivisions is needed. Besides issues of inadequate statistical power in most studies, which is a considerable problem because of the high degree of variability in anatomic brain measures,[13] none of the studies published to date has accounted for possible sources of confounding such as prior medication exposure. While future anatomic studies will focus on these issues, functional imaging studies are likely to become increasingly important in understanding the neural substrates of ADHD.

Can MRI Be Used to Diagnose ADHD?

MRI is not currently diagnostically useful in the routine assessment or management of ADHD. It is important to note that the anatomical differences noted are detected when looking at *groups* of children with and without ADHD. An individual may or may not have alterations in these brain areas. Although the brain imaging studies have been useful in helping us understand the key brain components involved in the illness, they are not currently specific enough to be used diagnostically.

If a child has a clinical history of ADHD but a normal brain scan, clinicians should not be deterred from treating. Conversely, if a child has no symptoms of ADHD but a brain scan consistent with what is found in groups of ADHD, treatment for ADHD is not indicated. Therefore, at the time of this writing, clinical history remains the gold standard of ADHD diagnosis.

There are several instances when brain imaging may be useful in the evaluation of ADHD:

1. when the ADHD symptomatology is accompanied by significant neurological abnormalities;
2. when there are comorbid psychotic features;
3. when the presentation is very atypical and unresponsive to conventional treatment approaches; or
4. in the case of identical twins where one has ADHD and the other does not.

So, although imaging is currently not of diagnostic utility in ADHD it may help to uncover the core neuropathology of the disease and may be useful in certain clinical situations. Imaging studies may help educate the families and the public that ADHD is a biological entity. Imaging may some day allow us to subclassify different types of ADHD, which may guide treatment interventions.

REFERENCES

1. BIEDERMAN, J. *et al.* 1992. Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder. Arch. Gen. Psychiatry **49:** 728–738.
2. MORRISON, J.R. & M.A. STEWART. 1973. Evidence for polygenetic inheritance in the hyperactive child syndrome. Am. J. Psychiatry **130:** 791–792.
3. WILLERMAN, L. 1973. Activity level and hyperactivity in twins. Child Dev. **44:** 288–293.
4. THAPAR, A. *et al.* 1995. Childhood hyperactivity scores are highly heritable and show sibling competition effects: twin study evidence. Behav. Genet. **25:** 537–544.

5. ALBERTS-CORUSH, J. *et al.* 1986. Attention and impulsivity characteristics of the biological and adoptive parents of hyperactive and normal control children. Am. J. Orthopsychiatry **56:** 413–423.
6. SOWELL, E.R. *et al.* 1999. Localizing age-related changes in brain structure between childhood and adolescence using statistical parametric mapping. Neuroimage **9:** 587–597.
7. SOWELL, E.R. *et al.* 1999. In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. Nat. Neurosci. **2:** 859–861.
8. GIEDD, J.N. *et al.* 1996. Quantitative magnetic resonance imaging of human brain development: ages 4–18. Cereb. Cortex **6:** 551–560.
9. REISS, A.L. *et al.* 1996. Brain development, gender and IQ in children. A volumetric imaging study. Brain **119:** 1763–1774.
10. PAUS, T. *et al.* 1999. Structural maturation of neural pathways in children and adolescents: in vivo study. Science **283:** 1908–1911.
11. HUTTENLOCHER, P.R. 1979. Synaptic density in human frontal cortex—developmental changes and effects of aging. Brain Res. **163:** 195–205.
12. HUTTENLOCHER, P.R. *et al.* 1997. Regional differences in synaptogenesis in human cerebral cortex. J. Comp. Neurol. **387:** 167–178.
13. LANGE, N. *et al.* 1997. Variability of human brain structure size: ages 4 to 20. Psychiatry Res. Neuroimaging **74:** 1–12.
14. CASTELLANOS, F.X. *et al.* 1996. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. Arch. Gen. Psychiatry **53:** 607–616.
15. ARNDT, S. *et al.* 1991. Problems with ratio and proportion measures of imaged cerebral structures. Bull. Clin. Neurosci. **55:** 131–136.
16. HYND, G.W. *et al.* 1991. Corpus callosum morphology in attention deficit-hyperactivity disorder: morphometric analysis of MRI. J. Learn. Dis. **24:** 141–146.
17. GIEDD, J.N. *et al.* 1994. Quantitative morphology of the corpus callosum in attention deficit hyperactivity disorder. Am. J. Psychiatry **151:** 665–669.
18. BAUMGARDNER, T.L. *et al.* 1996. Corpus callosum morphology in children with Tourette syndrome and attention deficit hyperactivity disorder. Neurology **47:** 477–482.
19. SEMRUD-CLIKEMAN, M. *et al.* 1994. Attention-deficit hyperactivity disorder: magnetic resonance imaging morphometric analysis of the corpus callosum. J. Am. Acad. Child Adolesc. Psychiatry **33:** 875–881.
20. OLSEN, P. *et al.* 1998. Psychological findings in preterm children related to neurologic status and magnetic resonance imaging. Pediatrics **102:** 329–336.
21. WEINBERGER, D.R. *et al.* 1982. Asymmetrical volumes of the right and left frontal and occipital regions of the human brain. Ann. Neurol. **11:** 97–100.
22. SHAYWITZ, B.A. *et al.* 1983. Attention deficit disorder: quantitative analysis of CT. Neurology **33:** 1500–1503.
23. HYND, G.W. *et al.* 1990. Brain morphology in developmental dyslexia and attention deficit disorder/hyperactivity. Arch. Neurol. **47:** 919–926.
24. FILIPEK, P.A. *et al.* 1997. Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. Neurology **48:** 589–601.
25. CASEY, B.J. *et al.* 1997. Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. Am. Acad. Child Adolesc. Psychiatry **36:** 374–383.
26. PONTIUS, A.A. 1973. Dysfunction patterns analogous to frontal lobe system and caudate nucleus syndromes in some groups of minimal brain dysfunction. J. Am. Med. Womens Assoc. **28:** 285–292.
27. HYND, G.W. *et al.* 1993. Attention deficit-hyperactivity disorder and asymmetry of the caudate nucleus. J. Child Neurol. **8:** 339–347.
28. MATARO, M. *et al.* 1997. Magnetic resonance imaging measurement of the caudate nucleus in adolescents with attention-deficit hyperactivity disorder and its relationship with neuropsychological and behavioral measures. Arch. Neurol. **54:** 963–968.
29. AYLWARD, E.H. *et al.* 1996. Basal ganglia volumes in children with attention-deficit hyperactivity disorder. J. Child Neurol. **11:** 112–115.

30. SINGER, H.S. *et al.* 1993. Volumetric MRI changes in basal ganglia of children with Tourette's syndrome. Neurology **43:** 950–956.
31. PETERSON, B. *et al.* 1993. Reduced basal ganglia volumes in Tourette's syndrome using three-dimensional reconstruction techniques from magnetic resonance images. Neurology **43:** 941–949.
32. NASRALLAH, H.A. *et al.* 1986. Cortical atrophy in young adults with a history of hyperactivity in childhood. Psychiatr. Res. **17:** 241–246.
33. BERQUIN, P.C. *et al.* 1998. Cerebellum in attention-deficit hyperactivity disorder: a morphometric MRI study. Neurology **50:** 1087–1093.
34. MOSTOFSKY, S.H. *et al.* 1998. Evaluation of cerebellar size in attention-deficit hyperactivity disorder. J. Child Neurol. **13:** 434–439.
35. JACOBSEN, L.K. *et al.* 1997. Quantitative morphology of the cerebellum and fourth ventricle in childhood-onset schizophrenia. Am. J. Psychiatry **154:** 1663–1669.
36. DELBELLO, M.P. *et al.* 1999. MRI analysis of the cerebellum in bipolar disorder: a pilot study. Neuropsychopharmacology **21:** 63–68.
37. DESMOND, J.E. *et al.* 1998. Dissociation of frontal and cerebellar activity in a cognitive task: evidence for a distinction between selection and search. Neuroimage **7:** 368–376.
38. SCHMAHMANN, J.D. *et al.* 1998. The cerebellar cognitive affective syndrome. Brain **121:** 561–579.
39. ZAMETKIN, A.J. *et al.* 1990. Cerebral glucose metabolism in adults with hyperactivity of childhood onset. N. Engl. J. Med. **323:** 1361–1366.
40. ZAMETKIN, A.J. *et al.* 1993. Brain metabolism in teenagers with attention-deficit hyperactivity disorder. Arch. Gen. Psychiatry **50:** 333–340.
41. ERNST, M. *et al.* 1994. Reduced brain metabolism in hyperactive girls. J. Am. Acad. Child Adolesc. Psychiatry **33:** 858–868.
42. ERNST, M. & A. ZAMETKIN. 1995. The interface of genetics, neuroimaging, and neurochemistry in attention-deficit hyperactivity disorder. *In* Psychopharmacology: The Fourth Generation of Progress. F.E. Bloom & D.J. Kupfer, Eds.: 1643–1652. Raven Press.
43. ERNST, M. *et al.* 1998. Age-related changes in brain glucose metabolism in adults with attention-deficit/hyperactivity disorder and control subjects. J. Neuropsychiatry Clin. Neurosci. **10:** 168–177.
44. LOU, H.C. *et al.* 1990. Focal cerebral dysfunction in developmental learning disabilities. Lancet **335:** 8–11.
45. AMEN, D.G. & J.H. PALDI. 1993. Evaluating ADHD with brain SPECT imaging. Biol. Psychiatry **33:** 44.
46. VAIDYA, C.J. *et al.* 1998. Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. Proc. Natl. Acad. Sci. USA **95:** 14494–14499.
47. RAPOPORT, J.L. *et al.* 1978. Dextroamphetamine: cognitive and behavioral effects in normal prepubertal boys. Science **199:** 560–563.
48. MEADOR-WOODRUFF, J.H. *et al.* 1994. Differential expression of autoreceptors in the ascending dopamine systems of the human brain. Proc. Natl. Acad. Sci. USA **91:** 8297–8301.
49. CASTELLANOS, F.X. 1997. Toward a pathophysiology of attention-deficit/hyperactivity disorder. Clin. Pediatrics **36:** 381–393.
50. SOLANTO, M.V. 1998. Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: a review and integration. Behav. Brain Res. **94:** 127–152.
51. SOLANTO, M.V. 1984. Neuropharmacological basis of stimulant drug action in attention deficit disorder with hyperactivity: a review and synthesis. Psychol. Bull. **95:** 387–409.
52. RUBIA, K. *et al.* 1999. Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. Am. J. Psychiatry **156:** 891–896.

53. SCHACHAR, R. *et al.* 1995. Test of four hypotheses for the comorbidity of attention-deficit hyperactivity disorder and conduct disorder. J. Am. Acad. Child Adolesc. Psychiatry **34:** 639–648.
54. LEVY, F. 1980. The development of sustained attention (vigilance) and inhibition in children: some normative data. J. Child Psychol. Psychiatry **21:** 77–84.
55. BUSH, G. *et al.* 1999. Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the counting Stroop. Biol. Psychiatry **45:** 1542–1552.
56. BUSH, G. *et al.* 1998. The counting Stroop: an interference task specialized for functional neuroimaging—validation study with functional MRI. Hum. Brain Mapping **6:** 270–282.
57. ERNST, M. *et al.* 1998. DOPA decarboxylase activity in attention deficit hyperactivity disorder adults. A [fluorine-18]fluorodopa positron emission tomographic study. J. Neurosci. **18:** 5901–5907.
58. ERNST, M. *et al.* 1999. High midbrain [^{18}F]DOPA accumulation in children with attention deficit hyperactivity disorder. Am. J. Psychiatry **156:** 1209–1215.
59. DOUGHERTY, D.D. *et al.* 1999. Dopamine transporter density in patients with attention deficit hyperactivity disorder. Lancet **354:** 2132–2133.
60. BARKLEY, R.A. 1998. Attention-deficit hyperactivity disorder. Sci. Am. **279:** 66–71.
61. GRAYBIEL, A.M. 1998. The basal ganglia and chunking of action repertoires. Neurobiol. Learn. Mem. **70:** 119–136.
62. JUEPTNER, M. *et al.* 1998. A review of differences between basal ganglia and cerebellar control of movements as revealed by functional imaging studies. Brain **121:** 1437–1449.
63. FULTON, J. 1951. Frontal Lobotomy and Affective Behavior. Norton. New York.
64. HEILMAN, K.M. *et al.* 1991. A possible pathophysiologic substrate of attention deficit hyperactivity disorder. J. Child Neurol. **6:** S76–S81.
65. BERGSTROM, K. *et al.* 1978. Computed tomography of the brain in children with minimal brain damage: a preliminary study of 46 children. Neuropaediatrie **9:** 378–384.
66. THOMPSON, J.S. *et al.* 1980. The role of computed axial tomography in the study of the child with minimal brain dysfunction. J. Learn. Disabil. **13:** 334–337.
67. CAPARULO, B.K. *et al.* 1981. Computed tomographic brain scanning in children with developmental neuropsychiatric disorders. J. Abnorm. Child Psychol. **20:** 338–357.
68. REISS, D. *et al.* 1983. Ventricular enlargement in child psychiatric patients: a controlled study with planimetric measurements. Am. J. Psychiatry **140**: 453–456.
69. HYND, G.W. *et al.* 1991. Corpus callosum morphology in attention deficit-hyperactivity disorder: morphometric analysis of MRI. J. Learn. Disabil. **24:** 141–146.
70. HYND, G.W. *et al.* 1993. Attention deficit hyperactivity disorder (ADHD) and asymmetry of the caudate nucleus. J. Child Neurol. **8:** 339–347.
71. AYLWARD, E.H. *et al.* 1996. Basal ganglia volumes in children with attention-deficit hyperactivity disorder. J. Child Neurol. **11:** 112–115.
72. CASEY, B.J. *et al.* 1997. Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. J. Am. Acad. Child Adolesc. Psychiatry **36:** 374–382.
73. MATARO, M. *et al.* 1997. Magnetic resonance imaging measurement of the caudate nucleus in adolescents with attention-deficit hyperactivity disorder and its relationship with neuropsychological and behavioral measures. Arch. Neurol. **54:** 963–968.
74. LOU, H.C. *et al.* 1984. Focal cerebral hypoperfusion in children with dysphasia and/or attention deficit disorder. Arch. Neurol. **41:** 825–829.
75. LOU, H.C. *et al.* 1989. Striatal dysfunction in attention deficit and hyperkinetic disorder. Arch. Neurol. **46:** 48–52.
76. MATOCHIK, J.A. *et al.* 1993. Effects of acute stimulant medication on cerebral metabolism in adults with hyperactivity. Neuropsychopharmacology **8:** 377–386.
77. MATOCHIK, J.A. *et al.* 1994. Cerebral glucose metabolism in adults with attention deficit hyperactivity disorder after chronic stimulant treatment. Am. J. Psychiatry **151:** 658–664.

neses for the comorbidity of attention-
isorder. J. Am. Acad. Child Adolesc.

attention (vigilance) and inhibition in
iol. Psychiatry **21:** 77–84.
dysfunction in attention-deficit/hyper-
counting Stroop. Biol. Psychiatry **45:**

interference task specialized for func-
unctional MRI. Hum. Brain Mapping **6:**

ctivity in attention deficit hyperactivity
positron emission tomographic study. J.

PA accumulation in children with atten-
ychiatry **156:** 1209–1215.
sporter density in patients with attention
132–2133.
ctivity disorder. Sci. Am. **279:** 66–71.
l chunking of action repertoires. Neuro-

nces between basal ganglia and cerebel-
functional imaging studies. Brain **121:**

ctive Behavior. Norton. New York.
physiologic substrate of attention deficit
S76–S81.
graphy of the brain in children with mini-
6 children. Neuropaediatrie **9:** 378–384.
puted axial tomography in the study of the
earn. Disabil. **13:** 334–337.
nographic brain scanning in children with
J. Abnorm. Child Psychol. **20:** 338–357.
nent in child psychiatric patients: a con-
ts. Am. J. Psychiatry **140:** 453–456.
norphology in attention deficit-hyperactiv-
I. J. Learn. Disabil. **24:** 141–146.
yperactivity disorder (ADHD) and asym-
rol. **8:** 339–347.
volumes in children with attention-deficit
: 112–115.
t frontostriatal circuitry in response inhibi-
sorder. J. Am. Acad. Child Adolesc. Psy-

nce imaging measurement of the caudate
icit hyperactivity disorder and its relation-
ral measures. Arch. Neurol. **54:** 963–968.
perfusion in children with dysphasia and/or
1: 825–829.
in attention deficit and hyperkinetic disor-

e stimulant medication on cerebral metabo-
sychopharmacology **8:** 377–386.
ose metabolism in adults with attention def-
stimulant treatment. Am. J. Psychiatry **151:**

78. ERNST, M. *et al.* 1994. Effects of intravenous dextroamphetamine on brain metabolism in adults with attention-deficit hyperactivity disorder (ADHD). Preliminary findings. Psychopharmacol. Bull. **30:** 219–225.
79. SIEG, K.G. *et al.* 1995. SPECT brain imaging abnormalities in attention deficit hyperactivity disorder. Clin. Nucl. Med. **20:** 55–60.
80. SCHWEITZER, J.B. *et al.* 1995. Regional cerebral blood flow during repeated exposure to a vigilance task in adults with attention deficit hyperactivity disorder. Soc. Neurosci. Abstr. **21:** 1926.
81. TEICHER, M.H. *et al.* 1996. Objective measurement of hyperactivity and attentional problems in ADHD. Am. Acad. Child Adolesc. Psychiatry **35:** 334–342.
82. SCHWEITZER, J.B. *et al.* 2000. Alterations in the functional anatomy of working memory in adult attention deficit hyperactivity disorder. Am. J. Psychiatry **157:** 278–280.
83. BUSH, G. *et al.* 1999. Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the counting Stroop. Biol. Psychiatry **45:** 1542–1552.